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Time to onset of gastrointestinal bleeding in the SUP-ICU trial: a preplanned substudy

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Conflicts of interest:
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Authors' contributions:
A.G. wrote the first draft. A.G. and T.L. conducted all statistical analyses. S.M. and M.K. were responsible for the SUP-ICU trial database. A.G., T.L., J.W. and M.H.M. drafted the protocol and statistical analysis plan. All authors contributed substantially to the SUP-ICU trial, the study protocol, this manuscript and approved the final version.

Abstract

Background
The aetiology and risk factors for clinically important gastrointestinal bleeding (CIB) in adult ICU patients may differ according to onset of CIB, which could affect the balance between benefits and harms of stress ulcer prophylaxis (SUP).

Methods
We assessed the time to CIB in the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial. We assessed if associations between baseline characteristics including allocation to SUP and CIB changed during time in the ICU, specifically in the later (after day two) compared to the earlier (first two days) period, using Cox models adjusted for SAPS II and allocation to SUP. Additionally, we described baseline characteristics and CIB episodes stratified by earlier/later/no CIB and 90-day mortality status.

Results
CIB occurred in 110/3291 (3.3%) patients after a median of 6 (interquartile range 2-13) days; 25.5% of the episodes occurred early. Higher SAPS II was consistently associated with increased risk of CIB (hazard ratio (HR) 1.03, 95% confidence interval (CI) 1.01-1.05 in the earlier period vs HR 1.02, 95% CI 1.01-1.03 in the later period; *P*=0.37); university hospital admission was associated with decreased risk of earlier CIB (HR 0.30, 95% CI 0.14-0.63); this significantly increased in the later period (to HR 0.85, 95% CI 0.53-1.37; *P*=0.02). Patients with later compared to earlier CIB received more transfusions and had more diagnostic/therapeutic procedures for CIB.

Conclusions
CIB mostly occurred more than two days after randomisation. University hospital admission was associated with significantly decreased risk of CIB in the earlier period only.

ClinicalTrials.gov registration: NCT02467621.

Editorial Comment

When gastrointestinal bleeding is likely to occur as a complication in critically ill patients is unclear. In this secondary analysis from this large trial trial of stress ulcer prophylaxis , the median time to bleeding detection was 6 days, and higher SAPS-II scores were associated with higher risk for bleeding.

Introduction

Intensive care unit (ICU) patients are at risk for stress-related gastrointestinal (GI) bleeding, which is associated with adverse outcomes including death.[1] In the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) inception cohort study conducted in 2013-2014, most ICU patients received stress ulcer prophylaxis (SUP) with acid suppressants,[2] as recommended in international guidelines.[3] Clinically important GI bleeding (CIB) occurs in 2-3% of ICU patients,[2] and stress ulcers are confirmed as the source of bleeding in less than half of critically ill patients with GI bleeding undergoing endoscopy.[4]

It has been suggested that SUP may increase the risk of nosocomial pneumonia, *Clostridium difficile* infections and cardiovascular events.[5,6] In a recent systematic review with meta-analysis and trial sequential analysis, SUP did not affect mortality.[7] SUP reduced overt GI bleeding and there was indication of, but not firm evidence for, a reduction in CIB.[7] Additionally, the effects on adverse events, pneumonia, *Clostridium difficile* infections and myocardial ischemia were uncertain.[7]

In the SUP-ICU inception cohort study, approximately half of the patients with CIB had onset of bleeding within the first two days in the ICU.[2] The aetiology and risk factors for earlier vs later GI bleeding may differ,[8] and differences in patients with earlier vs later CIB may affect the balance between benefits and harms of SUP.

The primary objectives of this study were to assess the time to CIB and whether the associations between use of SUP and baseline characteristics with CIB changed over time, specifically, in the earlier (first two days) vs later (day three or later) period. Secondary objectives were to describe baseline and bleeding episode characteristics in patients with earlier vs later CIB. We hypothesised that time to CIB would be similar to the SUP-ICU inception cohort study, that associations between allocation to SUP and baseline characteristics could change over time, and that outcomes and interventions used in patients with earlier vs later CIB could differ.

Methods

Study design, population and approvals

This preplanned, exploratory substudy of the SUP-ICU randomised clinical trial[9] (RCT) was conducted according to a protocol and statistical analysis plan finalised before the closure of the trial database on 21 March 2018 and subsequently published.[10] The manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[11] Additional methodological details and the completed STROBE checklist are presented in the **supplement**.

The SUP-ICU trial was an investigator-initiated, international, blinded, parallel-group RCT, which randomised adult patients acutely admitted to an ICU with one or more risk factors for GI bleeding to either 40 mg pantoprazole (SUP) or matching placebo intravenously once daily during ICU admission for a maximum of 90 days.[9]
The main exclusion criteria were previous GI bleeding during the index hospitalisation, ongoing treatment with acid suppressants, or contraindications to pantoprazole; detailed enrolment criteria are available in the **supplement** and elsewhere.[9,12,13] Patients were enrolled from 4 January 2016 through 22 October 2017, and all patients included in the primary analyses of the SUP-ICU trial were included in this substudy.

The SUP-ICU trial was approved by the Danish Health and Medicine Agency (2015030166), the Committee on Health Research Ethics in the Capital Region of Denmark (H-16036586; with additional local/national ethics approvals in the participating countries as appropriate),[12] by the Danish Data Protection Agency (RH-2015-3203695) and registered at ClinicalTrials.gov (NCT02467621).

Definitions

- Overt GI bleeding: one or more of the following: haematemesis; coffee ground emesis; melaena; haematochezia; bloody nasogastric aspirate.
- CIB: overt GI bleeding *and* at least one of the following criteria within 24 hours of overt GI bleeding and in the absence of other causes (clinical evaluation):
    1. decrease in systolic/diastolic/mean arterial blood pressure of ≥20 mmHg
    2. start of vasopressor or increase in vasopressor dose of ≥20%
    3. decrease in haemoglobin of ≥2 g/dL (1.24 mmol/L)
    4. transfusion of two or more units of red blood cells (RBCs).
- Earlier CIB: first CIB episode occurring within the first two days in the ICU after randomisation.
- Later CIB: first CIB episode occurring on the third day in the ICU after randomisation or later.

Earlier and later CIB were defined according to the distribution of CIB onset times in the SUP-ICU inception cohort study.[2,10] Additional variable definitions can be found in the **supplement** or the SUP-ICU publications.[9,10,12,13]

Outcomes

The primary outcome in this study was the time (number of days) to the first CIB episode.

Additionally, we studied the following secondary outcomes:

1. Vital status 90 days after randomisation
2. Number of days with CIB per patient

3. Number of days with overt GI bleeding per patient
4. Oesophago-gastro-duodenoscopy, laparotomy or coiling performed at least once on days with overt GI bleeding or CIB
5. Number of units of RBCs transfused on days with CIB per patient
6. Number of units of RBCs transfused in the ICU per patient

And the following *post-hoc* secondary outcomes:

7. Number of patients transfused with one or more units of RBCs on days with CIB
8. Number of patients transfused with one or more units of RBCs in the ICU
9. Number of patients with one or more overt GI bleeding episodes

Vital status was primarily obtained from regional/national registries, while all other outcomes were registered while patients were in the ICU, including readmissions or transfers to other participating ICUs.[9]

Statistics

We present baseline data descriptively for all patients stratified by bleeding status (earlier/later/no CIB) and vital status at day 90 (alive/dead). Numerical data are presented as medians with interquartile ranges (IQRs) and categorical data are presented as numbers with percentages.

Primary outcome and associations with baseline variables

We present the median (IQR) time to CIB in the full trial cohort and in each intervention group. We assessed the associations between baseline variables (including treatment allocation) and time to CIB using Cox proportional hazards models treating death before CIB as a competing event and thus censoring patients when they died.[14] Patients who were lost to follow-up for either CIB or mortality or who withdrew consent for further data registration were censored on the last day with available data.

Due to the limited number of CIB events, we conducted a number of different Cox models. In the first model, the association between allocation to pantoprazole (vs placebo) and CIB onset was assessed, while additional models assessed the effect of each additional baseline variable and CIB in turn.[10] Models were adjusted for treatment allocation and severity of illness using the Simplified Acute Physiology Score (SAPS) II[15]; the two models assessing these variables were only adjusted for the other variable.

We estimated hazard ratios (HRs) for CIB in the earlier and later periods and assessed possible differences between periods by including an interaction with time (later period - i.e. day three or later - vs earlier period) and the variable assessed in each model using a time transformation function.[16] Differences between periods are presented as HRs for the relative change in the later period compared to the earlier period along with P-values for the relative change.

Secondary outcomes

Detailed bleeding event characteristics are presented descriptively for all patients and stratified by bleeding status and vital status as described above. *Post-hoc*, we decided to also present these data for patients without CIB, and to present the number of patients fulfilling each of the four criteria for CIB, in total and stratified by bleeding status and vital status.

Sample size and general considerations

The sample size was fixed, as per the SUP-ICU trial,[9,12,13] and we expected approximately 100-120 patients with CIB.[2,10]

Two-tailed P-values <0.05 and 95% confidence intervals (CIs) not including 1.00 were considered statistically significant. We performed no corrections for multiple testing as all analyses presented in this study should be considered exploratory and hypothesis-generating.[10] All analyses were conducted using R version 3.5.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Missing data handling

We assessed the amount of missing data for all variables. As missingness for SAPS II was 7.6%[9] (**Table 1**), all Cox models were conducted using multiply imputed data[17-19] according to the protocol.[10] We generated 50 multiple imputed datasets using chained equations and included all baseline variables, treatment allocation, time to first CIB event and 90-day vital status in the imputation model. Complete case sensitivity analyses were also conducted.

Post-hoc sensitivity analyses

As the number of CIB events in the earlier period was lower than expected, we decided to conduct additional *post-hoc* analyses by repeating the Cox models after redefining the earlier and later periods according to the median number of days to the first CIB episode.

Results

We included all 3291 patients from the SUP-ICU trial who received trial medication and consented to use of data.[9]

Baseline demographic data stratified by CIB and vital status are presented in **Table 1**. Patients who either died before day 90 or had earlier CIB were older, and more patients with earlier CIB were admitted to non-university hospitals. There were no major differences in the number of comorbidities or risk factors between strata; however, more patients who developed earlier CIB had shock at randomisation and higher SAPS II, and more patients who developed CIB (regardless of onset) were on renal replacement therapy at randomisation.

Primary outcome

In total, 110/3291 (3.3%) patients experienced CIB; 41/1644 (2.5%) in the pantoprazole and 69/1647 (4.2%) in the placebo group. The median time to first CIB episode was 6 (IQR: 2 – 13) days overall; 6 (IQR: 2 – 11) days in the pantoprazole group and 6 (IQR: 3 – 13) days in the placebo group. The first CIB episode occurred in the earlier period in 28/110 (25.5%) patients with CIB (**Figure 1**).

The associations of baseline variables with CIB in the earlier period and the relative change in the later compared to the earlier period are presented in **Table 2**. In total, 109/3291 (3.3%) patients were censored for either CIB or mortality before day 90. Higher SAPS II was consistently associated with CIB with a HR (per point increase) of 1.03 (95% CI: 1.01 – 1.05) in the earlier period and a HR of 1.02 (95% CI: 1.01 – 1.03) in the later period (relative change in HR in the later compared to the earlier period: 0.99, 95% CI 0.96 – 1.01; *P* = 0.37). Admission to a university hospital was the only variable with a significant change in association with CIB according to time, with a HR of 0.30 (95% CI: 0.14 – 0.63) in the earlier period vs a HR of 0.85 (95% CI: 0.53 – 1.37) in the later period (relative change in HR in the later compared to the earlier period: 2.85, 95% CI: 1.18 – 6.90; *P* = 0.020).

A number of variables were associated with statistically significant increases or decreases in CIB risk in the later period, including allocation to pantoprazole (HR 0.51, 95% CI: 0.32 -0.80); emergency surgical admission (HR 0.48, 95% CI: 0.24 – 0.99); medical admission (HR 0.34, 95% CI: 0.17 – 0.69); renal replacement therapy (HR 2.35, 95% CI: 1.32 – 4.20); and SOFA score (HR 1.14, 95% CI: 1.05 – 1.24 per point increase).

None of these variables were associated with significantly increased or decreased risk in the earlier period or significant relative changes between periods.

Sensitivity analyses

The complete case sensitivity analyses were consistent with the primary analyses (**supplement Table S1**), as were most of the *post-hoc* sensitivity analyses (**supplement Table S2**).

Secondary outcomes

The overall 90-day mortality rate was 30.7%; 47.3% and 30.2% in patients with and without CIB, respectively. Detailed bleeding outcomes are presented in **Table 3**. More patients with CIB were transfused during the ICU stay, and patients with later CIB received more units of RBCs both during the ICU stay and on days with CIB. Additionally, patients with later CIB had more diagnostic or therapeutic procedures performed for CIB.

The number of patients who fulfilled each of the four criteria for CIB is presented in **supplement Table S3**.

Discussion

In this preplanned, exploratory substudy of the SUP-ICU trial, the median time to CIB was 6 (IQR 2 – 13) days, and later CIB was three times as common as earlier CIB. Higher SAPS II was consistently associated with increased risk of CIB, with no difference in the later compared to the earlier period. Admission to a university hospital was associated with lower CIB risk in the earlier period, while this association was significantly different with a relative increase in the later period. Patients with later CIB received more transfusions and had more diagnostic or therapeutic procedures performed for CIB than patients with earlier CIB.

Being admitted to a university hospital was the only variable that significantly differed in the later as compared to the earlier period. A possible explanation for this finding might be that the most complex patients are more frequently admitted to university hospital ICUs, and this group of patients have longer ICU stays. While we adjusted the analysis for SAPS II, differences in case-mix not accounted for by the limited comorbidity data in SAPS II may also explain the finding. Other potential explanations include ICU admission earlier during the course of illness in university hospitals, or that differences in research resources between university and non-university hospitals may have affected screening and randomisation. The increased number of transfusions and procedures in patients with later compared to earlier CIB may be explained to some extent by the former patients surviving longer.
The only variable that was consistently statistically significantly associated with CIB was SAPS II. The two most plausible explanations for the lack of consistent significant findings in the other analyses are the limited number of events in each period and consequent low power (especially the earlier period, which contained fewer events and fewer significant findings than the later period), but it could also be explained by the adjustment for SAPS II, as most other baseline variables are in some way associated with increased severity of illness. Of note, in the primary SUP-ICU results, allocation to pantoprazole led to fewer CIB events (relative risk 0.58, 95% CI 0.40 – 0.86).[9] This is consistent with the findings of this substudy, where pantoprazole was associated with significantly decreased CIB in the later period. Although the CIs for the earlier period and the relative change include no difference, it is interesting that point estimates suggest decreased CIB risk with PPI in both periods, but the largest effect in the later period.

The lower proportion of earlier CIB compared to the SUP-ICU inception cohort study[2] may be partially explained by the time from ICU admission to randomisation (median 15 (IQR: 5 – 28) and 14 (IQR: 6 – 23) hours in the pantoprazole and placebo groups, respectively).[9] Some patients may have experienced GI bleeding shortly after ICU admission leading to prescription of pantoprazole and exclusion from the SUP-ICU trial upon screening. The times to CIB in this study are more comparable to

estimates from a 20-year old RCT, where approximately 1 in 4 patients with CIB had their first CIB episode within five days after randomisation.[20]

Strengths and limitations

Strengths of this study reflect those of the SUP-ICU trial,[9] including the large sample size, pragmatic design, high external validity and data quality; our missing data handling strategy; and prepublication of the protocol and statistical analysis plan,[10] which increases transparency and trustworthiness.[21-24]

The study has a number of limitations too, and the results should be considered exploratory and hypothesis-generating as stated in the protocol.[10] First, despite the large size of the SUP-ICU trial, the number of CIB events was limited, as expected, which led to lower precision and a risk of not detecting true differences (type 2 errors). However, potential differences in associations in the two time periods that did not reach statistical significance due to low power are probably of limited clinical relevance due to the rarity of CIB. Second, as the SUP-ICU trial only included patients with at least one risk factor for GI bleeding, the results may not be directly transferable to ICU patients without any of these risk factors. Third, ICUs participating in the SUP-ICU trial may differ from ICUs not participating in how GI bleeding is recognised and treated. Fourth, our analysis strategy was relatively simple, only adjusted for two variables (SAPS II and allocation to pantoprazole), and only assessed time differences according to one point in time. Other adjustment strategies could have been considered, and associations with CIB if not adjusted for SAPS II or use of SUP may be different. However, the rarity of CIB would make more complex models fragile and conducting additional analyses would increase the risk of chance findings (type 1 errors). Fifth, while our definitions of earlier vs later CIB were based on previous research,[2] the cut-off of two days may be considered somewhat arbitrary. Importantly, though, results were similar in the sensitivity analyses conducted after redefining the time periods. Finally, the assessment of secondary outcomes according to time of first CIB event may be subject to survival bias and a competing risk of death before CIB[25], as the most severely ill patients may be more likely to develop CIB, but also more likely die before that happens. We did not account for this in the descriptive presentations of secondary outcome data.

In conclusion, half of all CIB events happened in the first week, and only a quarter of CIB events occurred in the earlier period. Higher SAPS II was consistently associated with increased risk of CIB, and admission to a university hospital was the only variable with a significantly different association in the time periods considered, with a decreased risk in the earlier period and a relatively increased risk in the later period. Patients with later CIB received more transfusions and had more diagnostic or therapeutic procedures performed for CIB than those with earlier CIB.

References

1. Cook DJ, Griffith LE, Walter SD, et al. The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. *Crit Care*. 2001;5:368-375.
2. Krag M, Perner A, Wetterslev J, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med*. 2015;41:833-845.
3. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43:304-377.
4. Cook D, Heyland D, Griffith L, et al. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. *Crit Care Med*. 1999;27:2812-2817.
5. MacLaren R, Reynolds PM, Allen RR. Histamine-2 Receptor Antagonists vs Proton Pump Inhibitors on Gastrointestinal Tract Hemorrhage and Infectious Complications in the Intensive Care Unit. *JAMA Intern Med*. 2014;174:564-574.
6. Charlot M, Ahlehoff O, Norgaard ML, et al. Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. *Ann Intern Med*. 2010;153:378-386.
7. Barbateskovic M, Marker S, Granholm A, et al. Stress ulcer prophylaxis with proton pump inhibitors or histamin-2 receptor antagonists in adult intensive care patients: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2019;45:143-158.
8. Mircea N, Jianu E, Constantinescu C, et al. Stress ulcers in intensive care (etiology, symptomatology and therapy). *Resuscitation*. 1984;12:59–76.
9. Krag M, Marker S, Perner A, et al. Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU. *N Engl J Med.* 2018;379:2199-2208.
10. Granholm A, Lange T, Anthon C, et al. Timing of onset of gastrointestinal bleeding in the ICU: Protocol for a preplanned observational study. *Acta Anaesthesiol Scand*. 2018;62:1165-1170.
11. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344–349.
12. Krag M, Perner A, Wetterslev J, et al. Stress ulcer prophylaxis in the intensive care unit trial: detailed statistical analysis plan. *Acta Anaesthesiol Scand*. 2017;61:859–868.
13. Krag M, Perner A, Wetterslev J, et al. Stress ulcer prophylaxis with a proton pump inhibitor versus placebo in critically ill patients (SUP-ICU trial): study protocol for a randomised controlled trial. *Trials.* 2016;17:205.
14. Beyersmann J, Allignol A, Schumacher M. Competing risks and multi-state models with R. New York: Springer; 2012.

15. Le Gall J-R, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993;270:2957-2963. [Erratum, *JAMA.* 1994;271:1321].
16. Therneau T, Crowson C, Atkinson E. Using Time Dependent Covariates and Time Dependent Coefficients in the Cox Model. Available at: https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf [Last accessed 13 May 2019]
17. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *BMC Med Res Methodol*. 2017;17:162.
18. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. *BMC Med Res Methodol*. 2009;9:57.
19. Vesin A, Azoulay E, Ruckly S, et al. Reporting and handling missing values in clinical studies in intensive care units. *Intensive Care Med*. 2013;39:1396–1404.
20. Cook D, Heyland D, Griffith L, Cook R, Marshall J, Pagliarello J. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *Crit Care Med*. 1999;27:2812–2817.
21. Dal-Ré R, Ioannidis JP, Bracken MB, et al. Making Prospective Registration of Observational Research a Reality. *Sci Transl Med*. 2014;6:224cm1.
22. Thomas L, Peterson ED. The Value of Statistical Analysis Plans in Observational Research. *JAMA*. 2012;308:773–774.
23. Loder E, Groves T, MacAuley D. Registration of observational studies. *BMJ*. 2010;340:c950.
24. The PLOS Medicine Editors. Observational studies: getting clear about transparency. *PLoS Med*. 2014;11:e1001711.
25. Colantuoni E, Scharfstein DO, Wang C, et al. Statistical methods to compare functional outcomes in randomized controlled trials with high mortality. *BMJ*. 2018;360:j5748.

Tables

Table 1 Baseline characteristics stratified by outcomes

Variable	All patients (n = 3291)	Earlier CIB and alive[a] (n = 16)	Earlier CIB and dead[a] (n = 12)	Later CIB and alive[a] (n = 42)	Later CIB and dead[a] (n = 40)	No CIB and alive[a] (n = 2215)	No CIB and dead[a] (n = 957)
Age (years)	67.0 (56.0 - 75.0)	71.0 (54.8 - 75.2)	74.0 (66.2 - 77.8)	64.0 (57.2 - 72.0)	71.5 (64.5 - 75.2)	65.0 (52.0 - 73.0)	72.0 (64.0 - 79.0)
Male gender	2106 (64.0%)	10 (62.5%)	7 (58.3%)	26 (61.9%)	28 (70.0%)	1440 (65.0%)	588 (61.4%)
Number of comorbidities[b]	0.0 (0.0 - 1.0)	0.0 (0.0 - 1.0)	1.0 (0.0 - 1.0)	0.0 (0.0 - 1.0)	0.0 (0.0 - 1.0)	0.0 (0.0 - 1.0)	0.0 (0.0 - 1.0)
Chronic lung disease[b]	657 (20.0%)	4 (25.0%)	6 (50.0%)	9 (21.4%)	7 (17.5%)	371 (16.7%)	260 (27.2%)
Previous myocardial infarction[b]	298 (9.1%)	0 (0.0%)	0 (0.0%)	5 (11.9%)	3 (7.5%)	174 (7.9%)	116 (12.1%)
Chronic heart failure (NYHA III-IV) [b]	199 (6.0%)	0 (0.0%)	0 (0.0%)	2 (4.8%)	2 (5.0%)	103 (4.7%)	91 (9.5%)
Immunosuppression[b]	62 (1.9%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (2.5%)	35 (1.6%)	25 (2.6%)
Haematological malignancy[b]	119 (3.6%)	1 (6.2%)	0 (0.0%)	1 (2.4%)	4 (10.0%)	56 (2.5%)	57 (6.0%)
Metastatic cancer[b]	111 (3.4%)	1 (6.2%)	1 (8.3%)	0 (0.0%)	3 (7.5%)	46 (2.1%)	60 (6.3%)
AIDS[b]	7 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)	4 (0.2%)	1 (0.1%)
Admitted to university hospital	2372 (72.1%)	9 (56.2%)	3 (25.0%)	32 (76.2%)	25 (62.5%)	1656 (74.8%)	638 (66.7%)
Time from ICU admission to randomisation (hours)	15.0 (5.0 - 26.0)	10.5 (2.8 - 25.8)	14.0 (4.5 - 21.2)	23.0 (10.0 - 40.8)	18.0 (6.5 - 35.2)	14.0 (5.0 - 26.0)	15.0 (5.0 - 26.0)
Admission type:							
- Elective surgical[c]	200 (6.1%)	1 (6.2%)	0 (0.0%)	6 (14.3%)	4 (10.0%)	139 (6.3%)	50 (5.2%)
- Emergency surgical	1048 (31.8%)	5 (31.2%)	3 (25.0%)	16 (38.1%)	14 (35.0%)	756 (34.1%)	249 (26.0%)
- Medical	2043 (62.1%)	10 (62.5%)	9 (75.0%)	20 (47.6%)	22 (55.0%)	1320 (59.6%)	658 (68.8%)
Number of risk factors[d]	2.0 (2.0 - 3.0)	2.0 (1.8 - 2.0)	2.0 (2.0 - 2.2)	2.0 (1.0 - 3.0)	2.0 (2.0 - 3.2)	2.0 (2.0 - 3.0)	2.0 (2.0 - 3.0)
Chronic liver disease[d]	94 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	2 (5.0%)	46 (2.1%)	43 (4.5%)
Chronic renal replacement therapy[d]	37 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	19 (0.9%)	18 (1.9%)
Acute coagulopathy[d]	577 (17.5%)	2 (12.5%)	1 (8.3%)	6 (14.3%)	13 (32.5%)	346 (15.6%)	209 (21.8%)
History of coagulopathy[d]	208 (6.3%)	0 (0.0%)	0 (0.0%)	2 (4.8%)	4 (10.0%)	117 (5.3%)	85 (8.9%)
Use of anticoagulants[d]	739 (22.5%)	2 (12.5%)	2 (16.7%)	10 (23.8%)	7 (17.5%)	443 (20.0%)	274 (28.6%)
Use of NSAID or acetylsalicylic acid[d]	533 (16.2%)	0 (0.0%)	2 (16.7%)	5 (11.9%)	4 (10.0%)	371 (16.7%)	150 (15.7%)

Use of intravenous thrombolysis[d]	47 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)	37 (1.7%)	8 (0.8%)
Invasive mechanical ventilation[d]	2589 (78.7%)	12 (75.0%)	9 (75.0%)	32 (76.2%)	31 (77.5%)	1739 (78.5%)	759 (79.3%)
Shock at inclusion[d]	2467 (75.0%)	14 (87.5%)	11 (91.7%)	31 (73.8%)	35 (87.5%)	1608 (72.6%)	762 (79.6%)
Renal replacement therapy at inclusion[d]	258 (7.8%)	3 (18.8%)	2 (16.7%)	5 (11.9%)	10 (25.0%)	147 (6.6%)	91 (9.5%)
SAPS II[e]	48.0 (38.0 - 59.0)	52.0 (41.5 - 58.0)	68.0 (60.8 - 77.0)	47.5 (36.0 - 55.2)	54.0 (47.0 - 65.5)	45.0 (36.0 - 56.0)	55.0 (45.0 - 66.0)
SOFA score[e]	9.0 (7.0 - 11.0)	8.0 (6.5 - 10.0)	11.0 (9.5 - 12.2)	9.0 (6.0 - 11.0)	11.0 (9.0 - 13.0)	8.0 (6.0 - 10.0)	10.0 (7.0 - 12.0)
Allocated to pantoprazole (vs placebo)	1644 (50.0%)	7 (43.8%)	6 (50.0%)	9 (21.4%)	19 (47.5%)	1116 (50.4%)	485 (50.7%)

Baseline data stratified by clinical outcomes. For detailed definitions, see **supplement** or elsewhere.[9,10,12,13]

[a] Stratified by any CIB episode (earlier/later/none) and vital status 90 days after inclusion. The 9 patients with missing vital status at day 90 are only included in the "All patients" column; none of these patients had CIB.

[b] The number of comorbidities includes all comorbidities marked with [b].

[c] Only acutely admitted patients were included; elective surgical patients were patients who had elective surgery in the seven days prior to ICU admission and were then acutely admitted to a participating ICU due to complications or events happening after the elective surgery, without fulfilment of the criteria for being classified as acute surgical admission.

[d] The number of risk factors includes all risk factors marked with [d].

[e] In total, 249 patients (7.6%) had missing data for SAPS II and 193 patients (5.9%) had missing data for the SOFA score. No data were missing for any other baseline variables presented in this table.

Abbreviations: AIDS: acquired immune deficiency syndrome; CIB: clinically important gastrointestinal bleeding; ICU: intensive care unit; NYHA: New York Heart Association functional classification; NSAID: non-steroidal anti-inflammatory drugs; SAPS II: Simplified Acute Physiology Score II; SOFA score: Sequential [Sepsis-related] Organ Failure Assessment score.

Table 2 Associations between baseline characteristics and CIB in the earlier and later periods

Variable	Hazard ratio in the earlier period (95% CI)	Hazard ratio in the later period (95% CI)	Relative change in hazard ratio in the later compared to the earlier period (95% CI)	P-value for test of change in association with time
Allocated to pantoprazole (vs placebo)	0.85 (0.40 – 1.78)	0.51 (0.32 – 0.80)	0.60 (0.25 – 1.42)	0.24
Age (per year)	1.01 (0.98 – 1.04)	1.01 (0.99 – 1.02)	1.00 (0.97 – 1.03)	0.85
Male gender	0.85 (0.40 – 1.82)	1.04 (0.66 – 1.64)	1.22 (0.50 – 2.95)	0.66
Number of comorbidities[a] (per comorbidity)	0.99 (0.59 – 1.69)	1.11 (0.82 – 1.51)	1.12 (0.61 – 2.06)	0.71
Admitted to university hospital	0.30 (0.14 – 0.63)	0.85 (0.53 – 1.37)	2.85 (1.18 – 6.90)	0.020
Time from ICU admission to randomisation (per hour)	0.99 (0.97 – 1.01)	1.00 (1.00 – 1.01)	1.01 (0.99 – 1.03)	0.17
Admission type: - Reference: elective surgical[b]				
- Emergency surgical	1.21 (0.15 – 9.73)	0.48 (0.24 – 0.99)	0.40 (0.04 – 3.59)	0.41
- Medical	1.38 (0.18 – 10.35)	0.34 (0.17 – 0.69)	0.25 (0.03 – 2.08)	0.20
Number of risk factors[c] (per risk factor)	0.80 (0.55 – 1.16)	1.08 (0.88 – 1.32)	1.36 (0.89 – 2.07)	0.16
Chronic liver disease[c]	Too few events[f]	Too few events[f]	Too few events[f]	Too few events[f]
Chronic renal replacement therapy[c]	Too few events[f]	Too few events[f]	Too few events[f]	Too few events[f]
Acute coagulopathy[c]	0.53 (0.16 – 1.76)	1.38 (0.83 – 2.32)	2.61 (0.71 – 9.61)	0.15
History of coagulopathy[c]	Too few events[f]	Too few events[f]	Too few events[f]	Too few events[f]
Use of anticoagulants[c]	0.54 (0.19 – 1.56)	0.89 (0.52 – 1.52)	1.64 (0.50 – 5.37)	0.41
Use of NSAID or acetylsalicylic acid[c]	0.40 (0.10 – 1.69)	0.62 (0.31 – 1.25)	1.55 (0.31 – 7.66)	0.59
Use of intravenous thrombolysis[c]	Too few events[f]	Too few events[f]	Too few events[f]	Too few events[f]
Invasive mechanical ventilation[c]	0.70 (0.29 – 1.64)	0.80 (0.48 – 1.34)	1.15 (0.42 – 3.12)	0.78
Shock at inclusion[c]	2.50 (0.75 – 8.30)	1.31 (0.76 – 2.27)	0.52 (0.14 – 1.95)	0.34
Renal replacement therapy at inclusion[c]	2.18 (0.82 – 5.78)	2.35 (1.32 – 4.20)	1.08 (0.35 – 3.31)	0.89
SAPS II (per point)	1.03 (1.01 – 1.05)	1.02 (1.01 – 1.03)	0.99 (0.96 – 1.01)	0.37
SOFA score (per point)	1.06 (0.94 – 1.21)	1.14 (1.05 – 1.24)	1.08 (0.94 – 1.23)	0.28

Associations between baseline variables and CIB according to time. All models assessed the association between each baseline variable and time to CIB in turn using Cox regressions adjusted for treatment allocation (pantoprazole vs placebo) and SAPS II, with an interaction term between the variable and time (specifically, assessing the relative change in association in the later compared to the earlier period).

[a] Number of comorbidities included the following comorbidities: chronic lung disease; previous myocardial infraction; chronic heart failure (NYHA III-IV); immunosuppression; haematological malignancy; metastatic cancer; and AIDS.
[b] Only acutely admitted patients were included; elective surgical patients were patients who had elective surgery in the seven days prior to ICU admission and were then acutely admitted to a participating ICU due to complications or events happening after the elective surgery, without fulfilment of the criteria for being classified as acute surgical admissions.
[c] Variables marked [c] are included in the number of risk factors.
[d] "Too few events" indicates that the analysis was not possible as no patients had both the variable and CIB in the earlier and/or later period.
Abbreviations: AIDS: acquired immune deficiency syndrome; CI: confidence interval; CIB: clinically important gastrointestinal bleeding; ICU: intensive care unit; NSAID: non-steroidal anti-inflammatory drugs; NYHA: New York Heart Association functional classification; SAPS II: Simplified Acute Physiology Score II; SOFA score: Sequential [Sepsis-related] Organ Failure Assessment score.

Table 3 Detailed bleeding outcome characteristics

Outcome	All patients (n = 3291)	Earlier CIB and alive[a] (n = 16)	Earlier CIB and dead[a] (n = 12)	Later CIB and alive[a] (n = 42)	Later CIB and dead[a] (n = 40)	No CIB and alive[a] (n = 2215)	No CIB and dead[a] (n = 957)
Number of days with CIB episodes in each patient	0.0 (0.0 - 0.0)	1.0 (1.0 - 2.2)	1.0 (1.0 - 1.0)	1.0 (1.0 - 2.0)	1.0 (1.0 - 3.0)	NA	NA
Number of days with overt GI bleeding episodes in each patient	0.0 (0.0 - 0.0)	1.5 (1.0 - 3.2)	1.0 (1.0 - 1.0)	2.0 (1.0 - 3.0)	1.0 (1.0 - 4.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)
Any procedure performed (oesophago-gastro-duodenoscopy/laparotomy/coiling)	50 (1.5%)	5 (31.2%)	1 (8.3%)	23 (54.8%)	19 (47.5%)	2 (0.1%)	0 (0.0%)
Number of units of red blood cells transfused on days with CIB per patient	0.0 (0.0 - 0.0)	1.0 (0.0 - 2.5)	1.5 (0.0 - 2.8)	2.0 (0.0 - 4.8)	2.0 (1.0 - 9.5)	NA	NA
Number of units of red blood cells transfused per patient	0.0 (0.0 - 1.0)	3.5 (0.0 - 8.0)	2.5 (0.8 - 6.2)	7.0 (2.2 - 14.0)	7.5 (2.8 - 19.2)	0.0 (0.0 - 1.0)	0.0 (0.0 - 1.0)
Any red blood cell transfusions on days with CIB	78 (2.4%)	8 (50.0%)	8 (66.7%)	30 (71.4%)	32 (80.0%)	NA	NA
Any red blood cell transfusions during ICU stay	1023 (31.1%)	10 (62.5%)	9 (75.0%)	35 (83.3%)	36 (90.0%)	624 (28.2%)	304 (31.8%)
Any overt GI bleeding episodes	236 (7.2%)	16 (100.0%)	12 (100.0%)	42 (100.0%)	40 (100.0%)	72 (3.3%)	54 (5.6%)

Detailed bleeding outcome characteristics during days in the intensive care unit in the 90 days following inclusion (secondary outcomes). No data were missing for any of the outcome variables presented in this table.

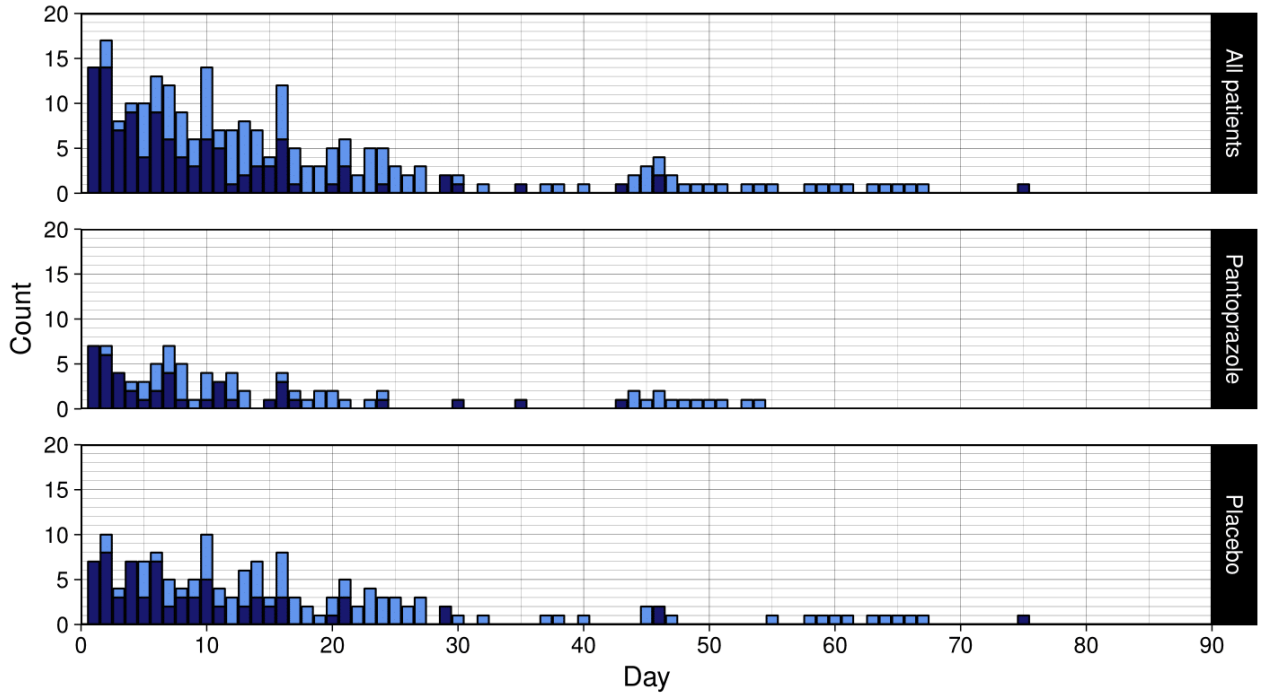
[a] Stratified by any CIB episode (earlier/later/none) and vital status 90 days after inclusion.

The 9 patients with missing vital status at day 90 are only included in the “All patients” column; none of these patients had CIB.

Abbreviations: CIB: clinically important gastrointestinal bleeding; GI: gastrointestinal; ICU: intensive care unit; NA: not applicable.

Figure titles and legends

Figure 1 Time of CIB episodes



Number of patients with CIB according to days from randomisation in the full trial cohort and stratified by treatment allocation. A similar figure for overt GI bleeding is presented in the **supplement**.
The dark part of each bar represents patients who had their first CIB episode on this day, the light part of each bar represents patients who had a CIB episode on this day but previously had another episode.
Abbreviations: CIB: clinically important gastrointestinal bleeding.